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Signed Andrew Gerrard

Dated 10 November 2003

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1/77

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
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1. Your reference
LRD-GB-3-421

25 APR 2003

0310890.9

2. Patent application number
(The Patent Office will fill in this part)

13MAY03 E806647-1 D10059
P01/7700 0.00-0310890.9

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

Rega Foundation, Minderbroedersstraat 10, 3000 Leuven

Represented by Prof. Dr. Erik De Clercq, President, Rega Foundation

Patents ADP number *(if you know it)*

07293589001

If the applicant is a corporate body, give the country/state of its incorporation

Belgium

4. Title of the invention

Glycopeptidic compounds

5. Name of your agent *(if you have one)*

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

K.U.Leuven R&D
care off:
Hubert Velge
Neaves Cottage
Neaves Lane - Glyndebourne
East Sussex BN8 5UA

Patents ADP number *(if you know it)*

08007916003

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	43
Claim(s)	1
Abstract	1
Drawing(s)	1

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	2
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	1 fax cover sheet 1 fee sheet with request for fax back service

11. I/We request the grant of a patent on the basis of this application.

Prof. Dr. Erik De Clercq — Signature — Date 24 April 2003

12. Name and daytime telephone number of person to contact in the United Kingdom: Hubert Velge, +44 7940 540 397

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

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Glycopeptidic Compounds

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The field of the invention comprises novel pharmaceuticals for preventing and treating antiviral infection, preferably retroviral infections and more preferably HIV infection.

BACKGROUND

Glycopeptide antibiotics (Vancomycin, Teicoplanin) are vital therapeutic agents used world-wide for the treatment of infections with gram-positive bacteria. Emerging bacterial resistance to vancomycin, which has recently become a major public health threat, is a stimulus for the synthesis and investigation of various derivatives of glycopeptide antibiotics (Malabarba, A et al Med. Res. Rev. 17: 69-137, 1997 and Pavlov A.Y. & M.N.Preobrazhenskaya. Russian Journal of Bioorganic Chemistry. 24:570 - 587, 1998). However, none of these compounds or their derivatives have been demonstrated to have antiviral properties or to be suitable to inhibit or prevent viral infections.

The present invention includes various new semisynthetic derivatives of natural glycopeptide antibiotics such as vancomycin, eremomycin, chloroeremomycin, teicoplanin, DA-40926 and others, their aglycons and also products of their partial degradation with the peptide core destroyed or modified in peptide core and in sugar moieties. The present derivatives are useful as anti-HIV compounds. They are particularly effective against drug-resistant HIV strains.

SUMMARY OF THE INVENTION

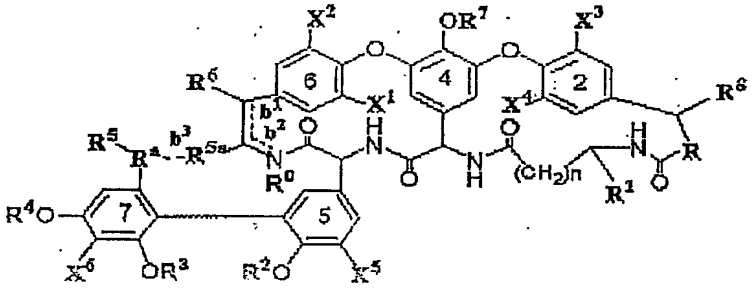
New semisynthetic derivatives of natural glycopeptide antibiotics have been designed and tested for antiviral activity and cell toxicity.

The invention includes novel compounds and methods of making novel compounds with pronounced anti-HIV activity and low cell toxicity, methods of structurally modifying said compounds for enhanced antiviral activity and methods of structurally modifying said compounds for decreasing or removing antibacterial activity while maintaining antiviral activity.

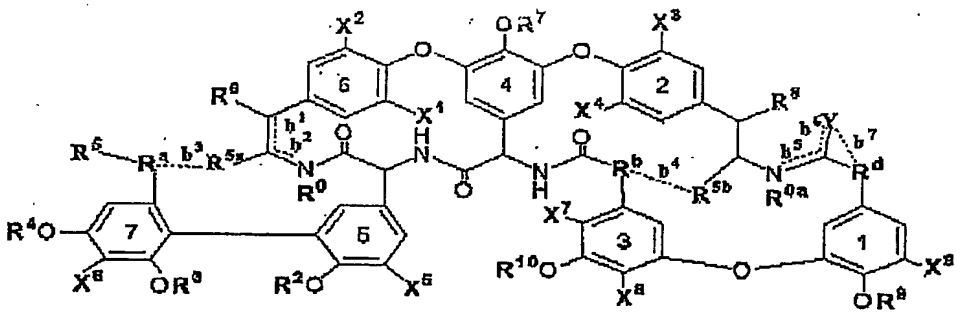
An embodiment of present invention comprises thus novel pharmaceuticals derived from glycopeptide antibiotics or from glycopeptides with an analogue structure for preventing and treating antiviral infection, preferably retroviral infections and more preferably HIV infection.

A preferred embodiment of present invention are compounds of the formula I, II and III

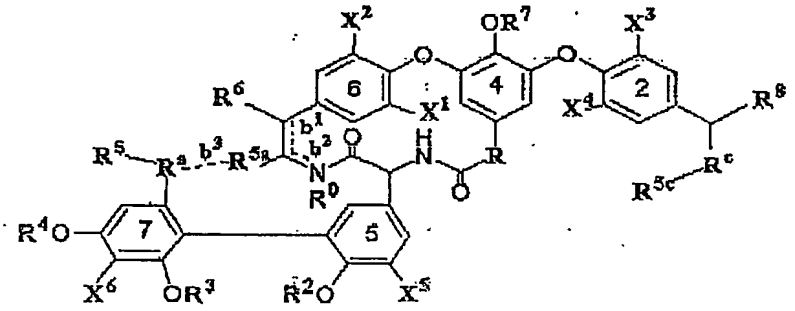
Formula I



Formula II



Formula III



wherein:

b^1 and b^2 each independently represents nihil or an additional bond, R^0 represents nihil when b^2 represents an additional bond and hydrogen when b^2 represents nihil, R^6 represents nihil when b^1 represents an additional bond and hydrogen when b^1 represents nihil, R^6 represents R^{6a} and R^0 represents hydrogen when b^1 and b^2 each represents nihil, wherein R^{6a} is described below. Preferably R^6 represents R^{6a}, R^0 represents hydrogen and b^1 and b^2 each represents nihil;

b^3 represents nihil or an additional bond, R^a---R^{5a} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_zN(R^{11a})CO$ when b^3 represents an additional bond, and R^a is R and R^{5a} is R^5 when b^3 represents nihil, wherein z is 0, 1, 2, 3 or 4 and R, R^5, R^{11} and R^{11a} are described below. Preferably R^a---R^{5a} represents CHNHCO;

b^4 represents nihil or an additional bond, R^b---R^{5b} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_pN(R^{11a})CO$ when b^4 represents an additional bond, and R^b is R and R^{5b} is R^5 when b^4 represents nihil, wherein p is 0, 1, 2, 3 or 4 and R, R^5 R^{11} and R^{11a} are described below;

b^5, b^6 and b^7 each independently represents nihil or an additional bond. Y represents oxygen, R^{0a} represents hydrogen and R^d represents R or a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5 and b^7 represent nihil and b^6 represents an additional bond. R^{0a} represents nihil, R^d—Y represents a group of the formula:

CHN=C(NR^{11})O or CHNHCON(R^{11}) when b^6 represents nihil and b^5 represents an additional bond. Y and R^{0a} each represents a hydrogen and R^d represents a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5, b^6 and b^7 each represents nihil, wherein q is 0, 1, 2, or 3 and R, R^{11} and R^{12} are described below;

n is 0, 1, 2 or 3;

X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen, halogen and X^6, wherein X^6 is defined below. Preferably X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen and Cl;

X^6 is selected from the group comprising hydrogen, halogen, SO_3H, OH, NO, NO_2, $NHNH_2$, NHN=CHR^{11}, N=NR^{11}, CHR^{11}R^{13}, $CH_2N(R^3)R^{11}$, R^3, R^{11} and R^{13}, wherein R^3 is CH_2 attached to phenolic hydroxyl group of the 7th amino acid, R^5, R^{11} and R^{13} are defined below. Preferably X^6 is CH_2R^{13};

X^8 is selected from hydrogen and methyl;

R^c represents R and R^{5c} represents R^5, wherein R and R^5 are defined below;

R is selected from CHR^{13} and R^{14}, wherein R^{13} and R^{14} are defined below. Preferably R is CHR^{13};

R^1 is selected from hydrogen and R^{11}, wherein R^{11} is defined below. Preferably R^1 is $(CH_2)_tCOOH$, $(CH_2)_tCONR^{11}R^{12}$, $(CH_2)_tCOR^{13}$, $(CH_2)_tCOOR^{11}$, COR^{15}, $(CH_2)_tOH$, $(CH_2)_tCN$, $(CH_2)_tR^{13}$, $(CH_2)_tSCH_3$, $(CH_2)_tSOCH_3$, $(CH_2)_tS(O)_2CH_3$, $(CH_2)_t$phenyl(*m*-OH, *p*-Cl), $(CH_2)_t$phenyl(*o*-X^7, *m*-OR^{10}, *p*-X^8)-[O-phenyl(*o*-OR^9, *m*-X^9, *m*-R^{16})]-*m*, where t is 0, 1, 2, 3 or 4. R, X^7, X^8, X^9 are defined above. R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are defined below;

R^2 and R^4 are each independently selected from hydrogen, R^{12} and R^{17}, wherein R^{12} and R^{17} are defined below;

R^3 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or O-acetylmannosyl. R^{12} and R^{17} are defined below;

R^5 is selected from COOH, COOR^{11}, COR^{13}, COR^{15}, CH_2OH, CH_2halogen, CH_2R^{13}, CHO, CH=NOR^{11}, CH=NNR^{11}R^{12} and C=NNHCONR^{11}R^{12}, wherein R^{11}, R^{12}, R^{13} and R^{15} are defined below;

R^{6a} is selected from OR^{12}, OR^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, ristosaminyl, N-acetylglucosaminyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, glucuronyl, 4-oxovancosaminyl, ureido-4-oxovancosaminyl and their derivatives with functional groups

such as, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^7 is selected from hydrogen, R^{12}, R^{17}, Sug and alkyl-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, mannosyl, ristosaminyl, N-acylglucosaminyl, N-acylglucuronyl, glucosaminyl, glucuronyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, acosaminyl, glucosyl-vancosaminyl, glucosyl-4-*epi*-vancosaminyl, glucosyl-3-*epi*-vancosaminyl, glucosyl-acosaminyl, glucosyl-ristosaminyl, glucosyl-actinosaminyl, glucosyl-rhamnosyl, glucosyl-olivosyl, glucosyl-mannosyl, glucosyl-4-oxovancosaminyl, glucosyl-ureido-4-oxovancosaminyl, glucosyl(rhamnosyl)-mannosyl-arabinosyl, glucosyl-2-O-Leu and their derivatives with as functional groups, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^8 is selected from hydrogen, R^{12}, R^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is O-mannosyl, O-galactosyl and O-galactosyl-galactosyl;

R^9 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is galactosyl or galactosyl-galactosyl. R^{12} and R^{17} are defined below;

R^{10} is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or fucosyl. R^{12} and R^{17} are defined below;

R^{11}, R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cyloalkyl, heterocycloalkyl;

R^{12} and R^{12a} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, acyl, amino-protecting group, carbamoyl, thiocarbamoyl, SO_2R^{11}, $S(O)R^{11}$, $COR^{13}\text{-}R^{18}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}NR^{11}R^{12}$ and $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above, R^{13} and R^{18} are defined below. Preferably R^{12a} is hydrogen, $COCHR^{18}NR^{11}R^{12}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$ and $COCHR^{18}R^{13}$;

R^{13} is selected from the group consisting of hydrogen, NHR^{12a}, $NR^{11}R^{12}$, $NR^{11}Sug$, $N^+R^{11}R^{11a}R^{11b}$, R^{15}, $NR^{11}C(R^{11a}R^{11b})COR^{15}$ and group of the formula:

N- A- N^+- A

wherein A is $-CH_2-B-CH_2-$ and B is $-(CH_2)_m-D-(CH_2)_r-$, wherein m and r are from 1 to 4 and D is O, S, NR^{12}, $N^+R^{11}R^{11a}$, wherein Sug is any cyclic or acyclic carbohydrate, R^{11}, R^{11a} and R^{12} are defined above;

R^{14} is CH_2, C=O, CHOH, C=NOR^{11}, CHNHOR^{11}, C=NNR^{11}R^{12}, C=NNHCONR^{11}R^{12} and CHNHNR^{11}R^{12}, wherein R^{11} and R^{12} are defined above;

R^{15} is selected from $N(R^{11})NR^{11a}R^{12}$, $N(R^{11})OR^{11a}$, $NR^{11}C(R^{11a}R^{11b})COR^{13}$, wherein R^{11}, R^{11a}, R^{11b}, R^{12} and R^{13} are defined above;

R^{16} is selected from group of the formula: R-R^5 or $CH(NH_2)CH_2OH$;

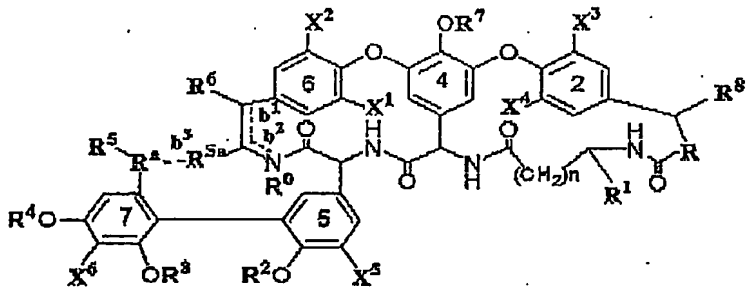
R^{17} is selected from SO_3H, $SiR^{11}R^{11a}R^{11b}$, $SiOR^{11}OR^{11a}OR^{11b}$, $PR^{11}R^{11a}$, $P(O)R^{11}R^{11a}$, $P^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above;

R^{18} is selected from hydrogen and R^1, wherein R^1 is defined above. Preferably R^{18} is CH_3, $CH_2CH(CH_3)_2$, phenyl(*p*-OH, *m*-Cl), phenyl-rhamnose-*p*, phenyl-(rhamnose-galactose)-*p*, phenyl-(galactose-galactose)-*p*, phenyl-O-methylrhamnose-*p*;

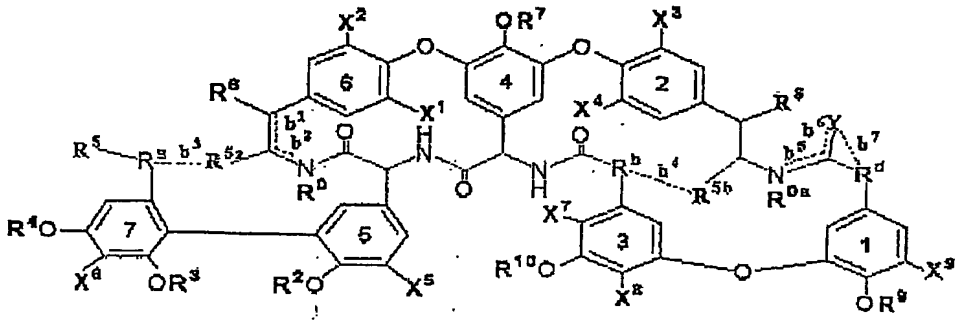
or a pharmaceutically acceptable salt thereof, for use in a therapeutic treatment or prophylactic treatment of viral infection

A more preferred embodiment of present invention is the use of compounds of the formula I, II and III

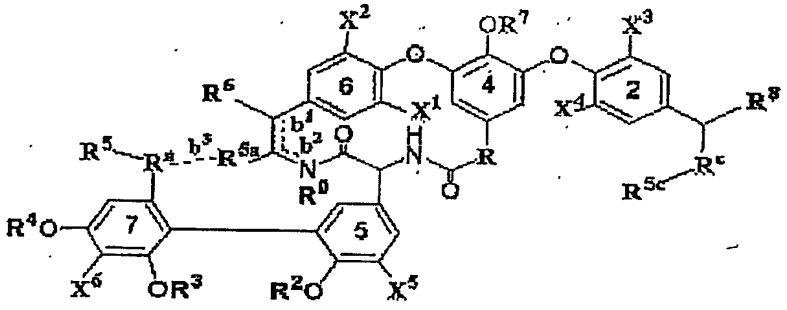
Formula I



Formula II



Formula III



wherein:

b^1 and b^2 each independently represents nihil or an additional bond, R^0 represents nihil when b^2 represents an additional bond and hydrogen when b^2 represents nihil, R^6 represents nihil when b^1 represents an additional bond and hydrogen when b^1 represents nihil, R^6 represents R^{6a} and R^0 represents hydrogen when b^1 and b^2 each represents nihil, wherein R^{6a} is described below. Preferably R^6 represents R^{6a}, R^0 represents hydrogen and b^1 and b^2 each represents nihil;

b^3 represents nihil or an additional bond, R^a---R^{5a} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_zN(R^{11a})CO$ when b^3 represents an additional bond, and R^a is R and R^{5a} is R^5 when b^3 represents nihil, wherein z is

0, 1, 2, 3 or 4 and R, R^5, R^{11} and R^{11a} are described below. Preferably R^a—R^{5a} represents CHNHCO;

b^4 represents nihil or an additional bond, R^b---R^{5b} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_2N(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_pN(R^{11a})CO$ when b^4 represents an additional bond, and R^b is R and R^{5b} is R^5 when b^4 represents nihil, wherein p is 0, 1, 2, 3 or 4 and R, R^5 R^{11} and R^{11a} are described below;

b^5, b^6 and b^7 each independently represents nihil or an additional bond. Y represents oxygen, R^{0a} represents hydrogen and R^d represents R or a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5 and b^7 represent nihil and b^6 represents an additional bond. R^{0a} represents nihil, R^d---Y represents a group of the formula: $CHN=C(NR^{11})O$ or $CHNHCON(R^{11})$ when b^6 represents nihil and b^5 represents an additional bond. Y and R^{0a} each represents a hydrogen and R^d represents group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5, b^6 and b^7 each represents nihil, wherein q is 0, 1, 2, or 3 and R, R^{11} and R^{12} are described below;

n is 0, 1, 2 or 3;

X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen, halogen and X^6, wherein X^6 is defined below. Preferably X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen and Cl;

X^6 is selected from the group comprising hydrogen, halogen, SO_3H, OH, NO, NO_2, $NHNH_2$, $NHN=CHR^{11}$, $N=NR^{11}$, $CHR^{11}R^{13}$, $CH_2N(R^3)R^{11}$, R^5, R^{11} and R^{13}, wherein R^3 is CH_2 attached to phenolic hydroxyl group of the 7th amino acid, R^5, R^{11} and R^{13} are defined below. Preferably X^6 is CH_2R^{13};

X^8 is selected from hydrogen and methyl;

R^c represents R and R^{5c} represents R^5, wherein R and R^5 are defined below;

R is selected from CHR^{13} and R^{14}, wherein R^{13} and R^{14} are defined below. Preferably R is CHR^{13};

R^1 is selected from hydrogen and R^{11}, wherein R^{11} is defined below. Preferably R^1 is $(CH_2)_tCOOH$, $(CH_2)_tCONR^{11}R^{12}$, $(CH_2)_tCOR^{13}$, $(CH_2)_tCOOR^{11}$, COR^{15}, $(CH_2)_tOH$, $(CH_2)_tCN$, $(CH_2)_tR^{13}$, $(CH_2)_tSCH_3$, $(CH_2)_tSOCH_3$, $(CH_2)_tS(O)_2CH_3$, $(CH_2)_t$phenyl(*m*-OH, *p*-Cl), $(CH_2)_t$phenyl(*o*-X^7, *m*-OR^{10}, *p*-X^8)-[O-phenyl(*o*-OR^9, *m*-X^9, *m*-R^{16})]-*m*, where t is 0, 1, 2, 3 or 4. R, X^7, X^8, X^9 are defined above. R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are defined below;

R^2 and R^4 are each independently selected from hydrogen, R^{12} and R^{17}, wherein R^{12} and R^{17} are defined below;

R^3 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or O-acetylmannosyl. R^{12} and R^{17} are defined below;

R^5 is selected from COOH, $COOR^{11}$, COR^{13}, COR^{15}, CH_2OH, CH_2halogen, CH_2R^{13}, CHO, $CH{=}NOR^{11}$, $CH{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$, wherein R^{11}, R^{12}, R^{13} and R^{15} are defined below;

R^{6a} is selected from OR^{12}, OR^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, ristosaminyl, N-acetylglucosaminyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, glucuronyl, 4-oxovancosaminyl, ureido-4-oxovancosaminyl and their derivatives with functional groups such as for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^7 is selected from hydrogen, R^{12}, R^{17}, Sug and alkyl-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, mannosyl, ristosaminyl, N-acylglucosaminyl, N-acylglucuronyl, glucosaminyl, glucuronyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, acosaminyl, glucosyl-vancosaminyl, glucosyl-4-*epi*-vancosaminyl, glucosyl-3-*epi*-vancosaminyl, glucosyl-acosaminyl, glucosyl-ristosaminyl, glucosyl-actinosaminyl, glucosyl-rhamnosyl, glucosyl-olivosyl, glucosyl-mannosyl, glucosyl-4-oxovancosaminyl, glucosyl-ureido-4-oxovancosaminyl, glucosyl(rhamnosyl)-mannosyl-arabinosyl, glucosyl-2-O-Leu and their derivatives with as functional groups, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^8 is selected from hydrogen, R^{12}, R^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is O-mannosyl, O-galactosyl and O-galactosyl-galactosyl;

R^9 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is galactosyl or galactosyl-galactosyl. R^{12} and R^{17} are defined below;

R^{10} is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or fucosyl. R^{12} and R^{17} are defined below;

R^{11}, R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cyloalkyl, heterocycloalkyl;

R^{12} and R^{12a} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, acyl, amino-protecting group, carbamoyl, thiocarbamoyl, SO_2R^{11}, $S(O)R^{11}$, COR^{13}-R^{18}, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}NR^{11}R^{12}$ and $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above, R^{13} and R^{18} are defined below. Preferably R^{12a} is hydrogen, $COCHR^{18}NR^{11}R^{12}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$ and $COCHR^{18}R^{13}$;

R^{13} is selected from the group consisting of hydrogen, NHR^{12a}, $NR^{11}R^{12}$, $NR^{11}Sug$, $N^+R^{11}R^{11a}R^{11b}$, R^{15}, $NR^{11}C(R^{11a}R^{11b})COR^{15}$ and group of the formula:

N- A- N^+- A

wherein A is $-CH_2$-B-CH_2- and B is $-(CH_2)_m$-D-$(CH_2)_r-$, wherein m and r are from 1 to 4 and D is O, S, NR^{12}, $N^+R^{11}R^{11a}$, wherein Sug is any cyclic or acyclic carbohydrate, R^{11}, R^{11a} and R^{12} are defined above;

R^{14} is CH_2, C=O, CHOH, $C=NOR^{11}$, $CHNHOR^{11}$, $C=NNR^{11}R^{12}$, $C=NNHCONR^{11}R^{12}$ and $CHNHNR^{11}R^{12}$, wherein R^{11} and R^{12} are defined above;

R^{15} is selected from $N(R^{11})NR^{11a}R^{12}$, $N(R^{11})OR^{11a}$, $NR^{11}C(R^{11a}R^{11b})COR^{13}$, wherein R^{11}, R^{11a}, R^{11b}, R^{12} and R^{13} are defined above;

R^{16} is selected from group of the formula: R-R^5 or $CH(NH_2)CH_2OH$;

R^{17} is selected from SO_3H, $SiR^{11}R^{11a}R^{11b}$, $SiOR^{11}OR^{11a}OR^{11b}$, $PR^{11}R^{11a}$, $P(O)R^{11}R^{11a}$, $P^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above;

R^{18} is selected from hydrogen and R^1, wherein R^1 is defined above. Preferably R^{18} is CH_3, $CH_2CH(CH_3)_2$, phenyl(*p*-OH, *m*-Cl), phenyl-rhamnose-*p*, phenyl-(rhamnose-galactose)-*p*, phenyl-(galactose-galactose)-*p*, phenyl-O-methylrhamnose-*p*;

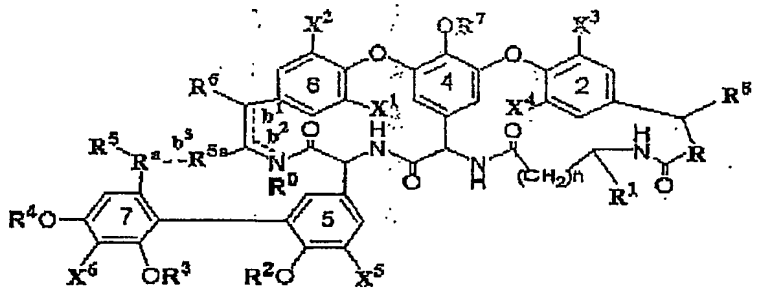
or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for preventing or treating viral infections.

Each compound of the present invention may be a pure stereoisomer coupled at each of its chiral centers or it may be inverted at one or more of its chiral centers. It may be a single stereoisomer or a mixture of two or more stereoisomers. If it is a mixture, the ratio may or may

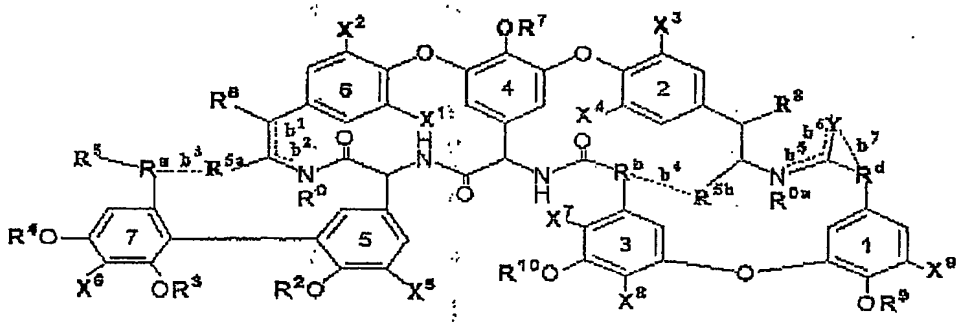
not be equimolar. Preferably the compound is a single stereoisomer. Preferably the stereochemistry of the peptide core of the compound containing six amino acids (2-7) is 2(*R*), 3(*S*), 4(*R*), 5(*R*), 6(*S*) and 7(*S*).

Yet another preferred embodiment of present invention are compounds of the formula I, II and III

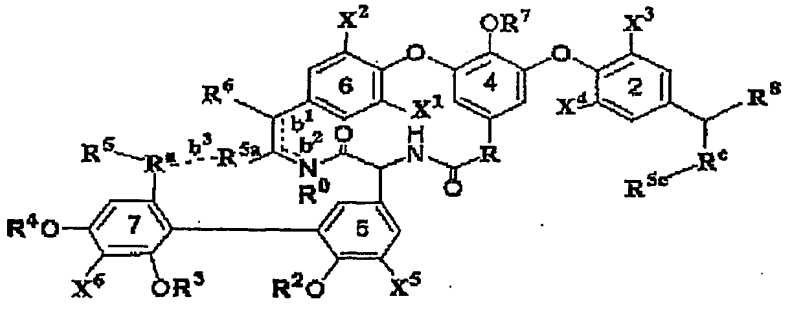
Formula I



Formula II



Formula III



wherein:

b^1 and b^2 each independently represents nihil or an additional bond, R^0 represents nihil when b^2 represents an additional bond and hydrogen when b^2 represents nihil, R^6 represents nihil when b^1 represents an additional bond and hydrogen when b^1 represents nihil, R^6 represents R^{6a} and R^0 represents hydrogen when b^1 and b^2 each represents nihil, wherein R^{6a} is described below. Preferably R^6 represents R^{6a}, R^0 represents hydrogen and b^1 and b^2 each represents nihil;

b^3 represents nihil or an additional bond, R^a---R^{5a} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_zN(R^{11a})CO$ when b^3 represents an additional bond, and R^a is R and R^{5a} is R^5 when b^3 represents nihil, wherein z is 0, 1, 2, 3 or 4 and R, R^5, R^{11} and R^{11a} are described below. Preferably R^a---R^{5a} represents CHNHCO;

b^4 represents nihil or an additional bond, R^b---R^{5b} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_pN(R^{11a})CO$ when b^4 represents an additional bond, and R^b is R and R^{5b} is R^5 when b^4 represents nihil, wherein p is 0, 1, 2, 3 or 4 and R, R^5 R^{11} and R^{11a} are described below;

b^5, b^6 and b^7 each independently represents nihil or an additional bond. Y represents oxygen, R^{0a} represents hydrogen and R^d represents R or a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5 and b^7 represent nihil and b^6 represents an additional bond. R^{0a} represents nihil, R^d---Y represents a group of the formula: $CHN=C(NR^{11})O$ or $CHNHCON(R^{11})$ when b^6 represents nihil and b^5 represents an additional bond. Y and R^{0a} each represents a hydrogen and R^d represents group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5, b^6 and b^7 each represents nihil, wherein q is 0, 1, 2, or 3 and R, R^{11} and R^{12} are described below;

n is 0, 1, 2 or 3;

X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen, halogen and X^6, wherein X^6 is defined below. Preferably X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen and Cl;

X^6 is selected from the group comprising hydrogen, halogen, SO_3H, OH, NO, NO_2, $NHNH_2$, $NHN=CHR^{11}$, $N=NR^{11}$, $CHR^{11}R^{13}$, $CH_2N(R^3)R^{11}$, R^5, R^{11} and R^{13}, wherein R^3 is CH_2 attached

to phenolic hydroxyl group of the 7th amino acid, R^5, R^{11} and R^{13} are defined below. Preferably X^6 is CH_2R^{13};

X^8 is selected from hydrogen and methyl;

R^c represents R and R^{5a} represents R^5, wherein R and R^5 are defined below;

R is selected from CHR^{13} and R^{14}, wherein R^{13} and R^{14} are defined below. Preferably R is CHR^{13};

R^1 is selected from hydrogen and R^{11}, wherein R^{11} is defined below. Preferably R^1 is $(CH_2)_tCOOH$, $(CH_2)_tCONR^{11}R^{12}$, $(CH_2)_tCOR^{13}$, $(CH_2)_tCOOR^{11}$, COR^{15}, $(CH_2)_tOH$, $(CH_2)_tCN$, $(CH_2)_tR^{13}$, $(CH_2)_tSCH_3$, $(CH_2)_tSOCH_3$, $(CH_2)_tS(O)_2CH_3$, $(CH_2)_t$phenyl(*m*-OH, *p*-Cl), $(CH_2)_t$phenyl(*o*-X^7, *m*-OR^{10}, *p*-X^8)-[O-phenyl(*o*-OR^9, *m*-X^9, *m*-R^{16})]-*m*, where t is 0, 1, 2, 3 or 4. R, X^7, X^8, X^9 are defined above. R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are defined below;

R^2 and R^4 are each independently selected from hydrogen, R^{12} and R^{17}, wherein R^{12} and R^{17} are defined below;

R^3 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or O-acetylmannosyl. R^{12} and R^{17} are defined below;

R^5 is selected from COOH, $COOR^{11}$, COR^{13}, COR^{15}, CH_2OH, CH_2halogen, CH_2R^{13}, CHO, $CH{=}NOR^{11}$, $CH{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$, wherein R^{11}, R^{12}, R^{13} and R^{15} are defined below;

R^{6a} is selected from OR^{12}, OR^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, ristosaminyl, N-acetylglucosaminyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, glucuronyl, 4-oxovancosaminyl, ureido-4-oxovancosaminyl and their derivatives with functional groups such as, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, O-R^{12}, O-R^{17}, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^7 is selected from hydrogen, R^{12}, R^{17}, Sug and alkyl-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, mannosyl, ristosaminyl, N-acylglucosaminyl, N-acylglucuronyl, glucosaminyl, glucuronyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, acosaminyl, glucosyl-vancosaminyl, glucosyl-4-*epi*-vancosaminyl, glucosyl-3-*epi*-vancosaminyl, glucosyl-acosaminyl, glucosyl-ristosaminyl, glucosyl-actinosaminyl, glucosyl-rhamnosyl, glucosyl-olivosyl, glucosyl-mannosyl, glucosyl-

4-oxovancosaminyl, glucosyl-ureido-4-oxovancosaminyl, glucosyl(rhamnosyl)-mannosyl-arabinosyl, glucosyl-2-O-Leu and their derivatives with as functional groups, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, O-R^{12}, O-R^{17}, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^8 is selected from hydrogen, R^{12}, R^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is O-mannosyl, O-galactosyl and O-galactosyl-galactosyl;

R^9 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is galactosyl or galactosyl-galactosyl. R^{12} and R^{17} are defined below;

R^{10} is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or fucosyl. R^{12} and R^{17} are defined below;

R^{11}, R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cyloalkyl, heterocycloalkyl;

R^{12} and R^{12a} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, acyl, amino-protecting group, carbamoyl, thiocarbamoyl, SO_2R^{11}, $S(O)R^{11}$, COR^{13}-R^{18}, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}NR^{11}R^{12}$ and $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above, R^{13} and R^{18} are defined below. Preferably R^{12a} is hydrogen, $COCHR^{18}NR^{11}R^{12}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$ and $COCHR^{18}R^{13}$;

R^{13} is selected from the group consisting of hydrogen, NHR^{12a}, $NR^{11}R^{12}$, $NR^{11}Sug$, $N^+R^{11}R^{11a}R^{11b}$, R^{15}, $NR^{11}C(R^{11a}R^{11b})COR^{15}$ and group of the formula:

N- A- N^+- A

wherein A is $-CH_2$-B-CH_2- and B is $-(CH_2)_m$-D-$(CH_2)_r-$, wherein m and r are from 1 to 4 and D is O, S, NR^{12}, $N^+R^{11}R^{11a}$, wherein Sug is any cyclic or acyclic carbohydrate, R^{11}, R^{11a} and R^{12} are defined above;

R^{14} is CH_2, C=O, CHOH, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$, $C{=}NNHCONR^{11}R^{12}$ and $CHNHNR^{11}R^{12}$, wherein R^{11} and R^{12} are defined above;

R^{15} is selected from $N(R^{11})NR^{11a}R^{12}$, $N(R^{11})OR^{11a}$, $NR^{11}C(R^{11a}R^{11b})COR^{13}$, wherein R^{11}, R^{11a}, R^{11b}, R^{12} and R^{13} are defined above;

R^{16} is selected from group of the formula: R-R^5 or $CH(NH_2)CH_2OH$;

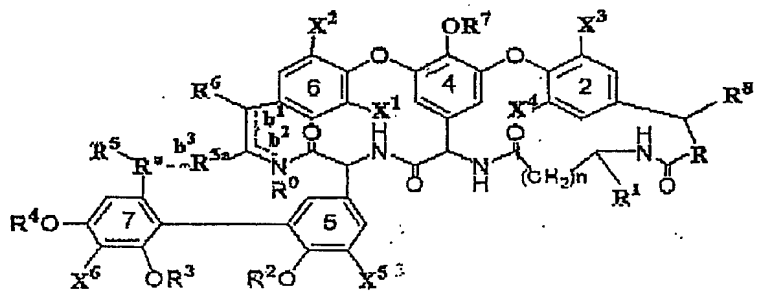
R^{17} is selected from SO_3H, $SiR^{11}R^{11a}R^{11b}$, $SiOR^{11}OR^{11a}OR^{11b}$, $PR^{11}R^{11a}$, $P(O)R^{11}R^{11a}$, $P^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above;

R^{18} is selected from hydrogen and R^1, wherein R^1 is defined above. Preferably R^{18} is CH_3, $CH_2CH(CH_3)_2$, phenyl(*p*-OH, *m*-Cl), phenyl-rhamnose-*p*, phenyl-(rhamnose-galactose)-*p*, phenyl-(galactose-galactose)-*p*, phenyl-O-methylrhamnose-*p*;

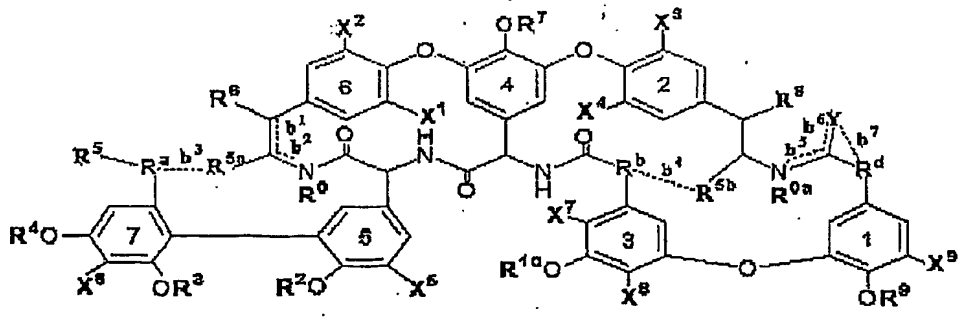
or a pharmaceutically acceptable salt thereof, for use in a treatment or preventive treatment of HIV infection, or of AIDS or of AIDS related complex.

Yet another preferred embodiment of present invention is the use of compounds of the formula I, II and III

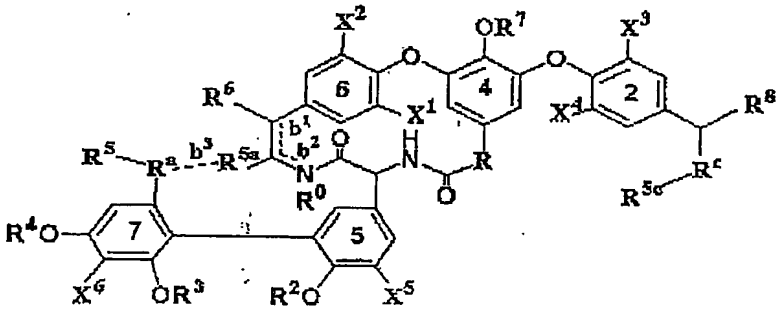
Formula I



Formula II



Formula III



wherein:

b^1 and b^2 each independently represents nihil or an additional bond, R^0 represents nihil when b^2 represents an additional bond and hydrogen when b^2 represents nihil, R^6 represents nihil when b^1 represents an additional bond and hydrogen when b^1 represents nihil, R^6 represents R^{6a} and R^0 represents hydrogen when b^1 and b^2 each represents nihil, wherein R^{6a} is described below. Preferably R^6 represents R^{6a}, R^0 represents hydrogen and b^1 and b^2 each represents nihil;

b^3 represents nihil or an additional bond, R^a---R^{5a} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_zN(R^{11a})CO$ when b^3 represents an additional bond, and R^a is R and R^{5a} is R^5 when b^3 represents nihil, wherein z is 0, 1, 2, 3 or 4 and R, R^5, R^{11} and R^{11a} are described below. Preferably R^a---R^{5a} represents CHNHCO;

b^4 represents nihil or an additional bond, R^b---R^{5b} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_pN(R^{11a})CO$ when b^4 represents an additional bond, and R^b is R and R^{5b} is R^5 when b^4 represents nihil, wherein p is 0, 1, 2, 3 or 4 and R, R^5 R^{11} and R^{11a} are described below;

b^5, b^6 and b^7 each independently represents nihil or an additional bond. Y represents oxygen, R^{0a} represents hydrogen and R^d represents R or a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5 and b^7 represent nihil and b^6 represents an additional bond. R^{0a} represents nihil, R^d—Y represents a group of the formula: $CHN=C(NR^{11})O$ or $CHNHCON(R^{11})$ when b^6 represents nihil and b^5 represents an additional

bond. Y and R^{0a} each represents a hydrogen and R^4 represents group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5, b^6 and b^7 each represents nihil, wherein q is 0, 1, 2, or 3 and R, R^{11} and R^{12} are described below;

n is 0, 1, 2 or 3;

X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen, halogen and X^6, wherein X^6 is defined below. Preferably X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen and Cl;

X^6 is selected from the group comprising hydrogen, halogen, SO_3H, OH, NO, NO_2, $NHNH_2$, $NHN{=}CHR^{11}$, $N{=}NR^{11}$, $CHR^{11}R^{13}$, $CH_2N(R^3)R^{11}$, R^5, R^{11} and R^{13}, wherein R^3 is CH_2 attached to phenolic hydroxyl group of the 7th amino acid, R^5, R^{11} and R^{13} are defined below. Preferably X^6 is CH_2R^{13};

X^8 is selected from hydrogen and methyl;

R^c represents R and R^{5c} represents R^5, wherein R and R^5 are defined below;

R is selected from CHR^{13} and R^{14}, wherein R^{13} and R^{14} are defined below. Preferably R is CHR^{13};

R^1 is selected from hydrogen and R^{11}, wherein R^{11} is defined below. Preferably R^1 is $(CH_2)_tCOOH$, $(CH_2)_tCONR^{11}R^{12}$, $(CH_2)_tCOR^{13}$, $(CH_2)_tCOOR^{11}$, COR^{15}, $(CH_2)_tOH$, $(CH_2)_tCN$, $(CH_2)_tR^{13}$, $(CH_2)_tSCH_3$, $(CH_2)_tSOCH_3$, $(CH_2)_tS(O)_2CH_3$, $(CH_2)_t$phenyl(*m*-OH, *p*-Cl), $(CH_2)_t$phenyl(*o*-X^7, *m*-OR^{10}, *p*-X^8)-[O-phenyl(*o*-OR^9, *m*-X^9, *m*-R^{16})]-*m*, where t is 0, 1, 2, 3 or 4. R, X^7, X^8, X^9 are defined above. R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are defined below;

R^2 and R^4 are each independently selected from hydrogen, R^{12} and R^{17}, wherein R^{12} and R^{17} are defined below;

R^3 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or O-acetylmannosyl. R^{12} and R^{17} are defined below;

R^5 is selected from COOH, $COOR^{11}$, COR^{13}, COR^{15}, CH_2OH, CH_2halogen, CH_2R^{13}, CHO, $CH{=}NOR^{11}$, $CH{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$, wherein R^{11}, R^{12}, R^{13} and R^{15} are defined below;

R^{6a} is selected from OR^{12}, OR^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, ristosaminyl, N-acetylglucosaminyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, glucuronyl, 4-oxovancosaminyl, ureido-4-oxovancosaminyl and their derivatives with functional groups such as, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives

comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^7 is selected from hydrogen, R^{12}, R^{17}, Sug and alkyl-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, mannosyl, ristosaminyl, N-acylglucosaminyl, N-acylglucuronyl, glucosaminyl, glucuronyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, acosaminyl, glucosyl-vancosaminyl, glucosyl-4-*epi*-vancosaminyl, glucosyl-3-*epi*-vancosaminyl, glucosyl-acosaminyl, glucosyl-ristosaminyl, glucosyl-actinosaminyl, glucosyl-rhamnosyl, glucosyl-olivosyl, glucosyl-mannosyl, glucosyl-4-oxovaneosaminyl, glucosyl-ureido-4-oxovancosaminyl, glucosyl(rhamnosyl)-mannosyl-arabinosyl, glucosyl-2-O-Leu and their derivatives with functional groups such as, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^8 is selected from hydrogen, R^{12}, R^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is O-mannosyl, O-galactosyl and O-galactosyl-galactosyl;

R^9 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is galactosyl or galactosyl-galactosyl. R^{12} and R^{17} are defined below;

R^{10} is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or fucosyl. R^{12} and R^{17} are defined below;

R^{11}, R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cyloalkyl, heterocycloalkyl;

R^{12} and R^{12a} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, acyl, amino-protecting group, carbamoyl, thiocarbamoyl, SO_2R^{11}, $S(O)R^{11}$, $COR^{13}\text{-}R^{18}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}NR^{11}R^{12}$ and $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above, R^{13} and R^{18} are defined below. Preferably R^{12a} is hydrogen, $COCHR^{18}NR^{11}R^{12}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$ and $COCHR^{18}R^{13}$;

R^{13} is selected from the group consisting of hydrogen, NHR^{12a}, $NR^{11}R^{12}$, $NR^{11}Sug$, $N^+R^{11}R^{11a}R^{11b}$, R^{15}, $NR^{11}C(R^{11a}R^{11b})COR^{15}$ and group of the formula:

N- A- N^+- A

wherein A is $-CH_2-B-CH_2-$ and B is $-(CH_2)_m-D-(CH_2)_r-$, wherein m and r are from 1 to 4 and D is O, S, NR^{12}, $N^+R^{11}R^{11a}$, wherein Sug is any cyclic or acyclic carbohydrate, R^{11}, R^{11a} and R^{12} are defined above;

R^{14} is CH_2, C=O, CHOH, $C=NOR^{11}$, $CHNHOR^{11}$, $C=NNR^{11}R^{12}$, $C=NNHCONR^{11}R^{12}$ and $CHNHNR^{11}R^{12}$, wherein R^{11} and R^{12} are defined above;

R^{15} is selected from $N(R^{11})NR^{11a}R^{12}$, $N(R^{11})OR^{11a}$, $NR^{11}C(R^{11a}R^{11b})COR^{13}$, wherein R^{11}, R^{11a}, R^{11b}, R^{12} and R^{13} are defined above;

R^{16} is selected from group of the formula: R-R^5, $CH(NH_2)CH_2OH$ or CH ;

R^{17} is selected from SO_3H, $SiR^{11}R^{11a}R^{11b}$, $SiOR^{11}OR^{11a}OR^{11b}$, $PR^{11}R^{11a}$, $P(O)R^{11}R^{11a}$, $P^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above;

R^{18} is selected from hydrogen and R^1, wherein R^1 is defined above. Preferably R^{18} is CH_3, $CH_2CH(CH_3)_2$, phenyl(*p*-OH, *m*-Cl), phenyl-rhamnose-*p*, phenyl-(rhamnose-galactose)-*p*, phenyl-(galactose-galactose)-*p*, phenyl-O-methylrhamnose-*p*;

for the preparation of a medicament for preventing infection of HIV, or treating infection by HIV or for treating AIDS or AIDS related complex.

Each compound of the present invention may be a pure stereoisomer coupled at each of its chiral centers or it may be inverted at one or more of its chiral centers. It may be a single stereoisomer or a mixture of two or more stereoisomers. If it is a mixture the ratio may or may not be equimolar. Preferably the compound is a single stereoisomer. Preferably the stereochemistry of the peptide core of the compound containing six amino acids (2-7) is 2(*R*), 3(*S*), 4(*R*), 5(*R*), 6(*S*) and 7(*S*).

The above mentioned compounds may be engineered to be inactive antibacterials at therapeutically effective antiviral doses and it also has been demonstrated by this invention that they can be engineered to have no mammalian cell toxicity at therapeutically effective antiviral doses. Yet another preferred embodiment of present invention includes thus the use in a prophylactic treatment or therapeutic treatment or the use to manufacture a medicament to treat therapeutically or prophylacticly a viral infection with vancomycin derivatives, eremomycin dervatives, eremomycin aglycon derivatives, Des-(N-methyl –D-leucyl)-ermycin aglycon, DMDA40, DA40, DA40 derivatives, DMDA40 derivatives, teicoplanin aglycon

derivatives, modified products of teicoplanin aglycon degradation or other structurally related glycopeptide antibiotics. The compounds are selected for antiviral activity and low mammalian cell toxicity and may be eventually selected as additional property antibacterial inactivity in antiviral activity assays such as the anti-HIV assays of present invention, a cytostatic activity assay of the state of the art or the cytostatic activity assay on the mammalian cell lines (L1210, Molt4/C8 or CEM) of present invention and additional antibacterial assays of the state of the art .

The compounds of the present invention for use in a prophylactic treatment or therapeutic treatment or the use to manufacture a medicament to treat therapeutically or prophylactically a viral infection, and preferably a retroviral infection and yet more preferably a HIV infection can be selected from the group of compounds 1to 30 of the examples of this application.

DESCRIPTION

Definitions

As used herein, the term **"halogen"** refers to Cl, Br, I, F.

The term "alkyl" refers to straight or branched, substituted or unsubstituted, saturated or unsaturated C_1-C_{24} hydrocarbon chains without or with suitable heteroatoms. The number and position of unsaturated bonds and heteroatoms may be varied. Any heteroaoms may be the same or different and can, for example, be O, N, S or B. The nature, number and position of substituents may be varied. Any substituents may be the same or different and can, for example, be halogen, SH, OH, COOH, NO_2, NH_2, $NHC(NH_2)=NH$, $CH(NH_2)=NH$, NHOH, $NHNH_2$, N_3, NO, CN, $N=NR^{11}$, $N=NR^{12}$, SOR^{11}, SO_2R^{11}, $B(OH)_2$, $B(OR^{11})_2$, CO, CHO, O-Sug, NR^{11}-Sug, R^{11}, R^{12}, R^{17} and R^{18}, wherein R^{11}, R^{12}, R^{17} and R^{18} are described as above and Sug is any cyclic or acyclic carbohydrate. Any substituents may themselves be substituted. The position, and number of any substituents may be varied.

The term **"cycloalkyl"**, as used herein, refers to saturated or unsaturated, substituted or unsubstituted monocyclic, bicyclic, tricyclic and macrocyclic C_2-C_{24} hydrocarbon chains. The nature, number and position of substituents may be varied. Any substituents may be the same or different and can, for example, be halogen, SH, OH, COOH, NO_2, NH_2, $NHC(NH_2)=NH$, $CH(NH_2)=NH$, NHOH, $NHNH_2$, N_3, NO, CN, $N=NR^{11}$, $N=NR^{12}$, SOR^{11}, SO_2R^{11}, $B(OH)_2$,

$B(OR^{11})_2$, CO, CHO, O-Sug, NR^{11}-Sug, R^{11}, R^{12}, R^{17} and R^{18}, wherein R^{11}, R^{12}, R^{17} and R^{18} are described as above and Sug is any cyclic or acyclic carbohydrate. Any substituents may themselves be substituted. The position, and number of any substituents may be varied. Typical cycloalkyls include cyclopropyl, cyclobutyl, cyclopentenyl, cyclopentyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclododecyl, bicylcopentyl, bicyclohexyl, bicycloheptyl, adamantyl, bornyl, norbornyl and the like.

The term **"heterocycloalkyl"**, as used herein, refers to saturated or unsaturated, substituted or unsubstituted monocyclic, bicyclic, tricyclic and macrocyclic C_2-C_{24} hydrocarbon chains with suitable heteroatoms selected from S, O, N or B. The nature, number and position of substituents may be varied. Any substituents may be the same or different and can, for example, be halogen, SH, OH, COOH, NO_2, NH_2, $NHC(NH_2)=NH$, $CH(NH_2)=NH$, NHOH, $NHNH_2$, N_3, NO, CN, $N=NR^{11}$, $N=NR^{12}$, SOR^{11}, SO_2R^{11}, $B(OH)_2$, $B(OR^{11})_2$, CO, CHO, O-Sug, NR^{11}-Sug, R^{11}, R^{12}, R^{17} and R^{18}, wherein R^{11}, R^{12}, R^{17} and R^{18} are described as above and Sug is any cyclic or acyclic carbohydrate. Any substituents may themselves be substituted. The position, and number of any substituents may be varied. Typical heterocycloalkyls include piperazinyl, piperidinyl, morpholinyl, quinuclidinyl, borabicyclononyl, crown ethers, azacrowns, thiacrowns and the like.

The term **"aryl"**, as used herein, refers to a stable, saturated or unsaturated, substituted or unsubstituted, C_6 membered organic monocyclic ring; a stable, saturated or unsaturated, substituted or unsubstituted, C_9-C_{10} membered organic fused bicyclic ring; a stable, saturated or unsaturated, substituted or unsubstituted, C_{12}-C_{14} membered organic fused tricyclic ring; or a stable, saturated or unsaturated, substituted or unsubstituted, C_{14}-C_{16} membered organic fused tetracyclic ring. Preferably the aryl is substituted by one or more moieties independently selected from the group comprising hydrogen, halogen, SH, OH, COOH, NO_2, NH_2, $NHC(NH_2)=NH$, $CH(NH_2)=NH$, NHOH, $NHNH_2$, N_3, NO, CN, $N=NR^{11}$, $N=NR^{12}$, SOR^{11}, SO_2R^{11}, $B(OH)_2$, $B(OR^{11})_2$, CO, CHO, O-Sug, NR^{11}-Sug, R^{11}, R^{12}, R^{17} and R^{18}, wherein R^{11}, R^{12}, R^{17} and R^{18} are described as above and Sug is any cyclic or acyclic carbohydrate. Any substituents may themselves be substituted. The position, and number of any substituents may be varied. Typical aryls include phenyl, biphenyl, triphenyl, naphtyl, fluorenyl, phenanthrenyl and the like.

The term "**heteroaryl**", as used herein, refers to a stable, saturated or unsaturated, substituted or unsubstituted, C_4-C_7 membered organic monocyclic ring having a heteroatom selected from S, O, and N; a stable, saturated or unsaturated, substituted or unsubstituted, C_9-C_{10} membered organic fused bicyclic ring having one or more heteroatoms selected from S, O, and N; or a stable, saturated or unsaturated, substituted or unsubstituted, C_{12}-C_{14} membered organic fused tricyclic ring having one or more heteroatoms selected from S, O, and N. The nitrogen and sulfur atoms of these rings are optionally oxidized, and the nitrogen heteroatoms are optionally quarternized. Preferably the aryl is substituted by one or more moieties independently selected from the group comprising hydrogen, halogen, SH, OH, COOH, NO_2, NH_2, $NHC(NH_2)=NH$, $CH(NH_2)=NH$, NHOH, $NHNH_2$, N_3, NO, CN, $N=NR^{11}$, $N=NR^{12}$, SOR^{11}, SO_2R^{11}, $B(OH)_2$, $B(OR^{11})_2$, CO, CHO, O-Sug, NR^{11}-Sug, R^{11}, R^{12}, R^{17} and R^{18}, wherein R^{11}, R^{12}, R^{17} and R^{18} are described as above and Sug is any cyclic or acyclic carbohydrate. Any substituents may themselves be substituted. The position, and number of any substituents may be varied. Typical heteroaryls include indolyl, quinolyl, piperidyl, thienyl, piperonyl, oxafluorenyl, pyridyl and benzothienyl and the like.

The term "**acyl**", as used herein, refers to group of the formula: $-COR^{11}$, $-COOR^{11}$ or $-CSR^{11}$ wherein R^{11} is described above.

The term "**carbamoyl**", as used herein, refers to group of the formula: $-CONR^{11}R^{11a}$ or $-CONHR^{12}$ wherein R^{11}, R^{11a} and R^{12} are described above.

The term "**thiocarbamoyl**" refers to group of the formula: $-CSNHR^{12}$ or $-C^{+}(SR^{11})NHR^{12}$, wherein R^{11} and R^{12} are described above.

The term "amino-protecting group" refers to those groups known in the art to be suitable for protecting the amino group during the acylation reaction. Such groups are well recognized, and selecting a suitable group for this purpose will be apparent. The tert-butoxycarbonyl (Boc), adamantyloxycarbonyl (Adoc), fluorenylmethoxycarbonyl (Fmoc) and carbobenzoxycarbonyl (Cbz) groups are examples of suitable amino-protecting groups.

The term "**carbohydrate**" refers to any cyclic or acyclic carbohydrate.

The term **"glycopeptide antibiotics"** refers to the natural glycopeptide antibiotics (glycopeptidic molecules produced by microorganisms such as actinomycetes with antibacterial activity) such as vancomycin, teicoplanin, eremomycin, DMDA40, DA40, their aglycon derivatives and various other structurally related glycopeptide antibiotics and semisynthetic derivatives.

Illustrative embodiments of the invention

The terminology used herein is not intended to limit the scope of the present invention but for the purpose of describing particular embodiments. This invention is not limited to the particular methodology, protocols and reagents described as these may vary.

The present invention includes a class of natural glycopeptide antibiotics and their derivatives and a class of compounds with structural similarity to said natural glycopeptide antibiotics which possess antiviral activity such as the anti-retroviral activity of presented examples. The invention also includes derivatives of glycopeptide antibiotics, which have been structurally engineered or modified to decrease or remove completely or partially the antibacterial activity while still comprising antiviral activity. The glycopeptide antibiotics are well known as powerful antibacterial agents against a wide variety of gram-positive bacteria and until now there is no data available about anti-viral, anti-retroviral or anti-HIV activity of such compounds. Several natural peptide antibiotics such as complestatins and chloropeptins with activity against HIV-1 (K. Matsuzara, H. et al J.Antibiotics 1994, V.47, N.10, p.1173-1174) and kistamycins with activity against influenza virus (N. Naruse, O, et al J. Antibiotics 1993, V.46, N.12, p.1812-1818) have been described. However the structures of these hexa- or heptapeptide antibiotics and the structures of glycopeptide antibiotics and of the aglycons of glycopeptide antibiotics have serious differences in both amino acid sequence and stereochemistry. All kystamycins, complestatin and chloropeptins contain a tryptophan moiety linked to central amino acid No 4, whereas it is represented by a substituted phenylalanine moiety in vancomycin, eremomycin, chloroeremomycin, teicoplanin, DA-40926 and other antibacterial glycopeptides.

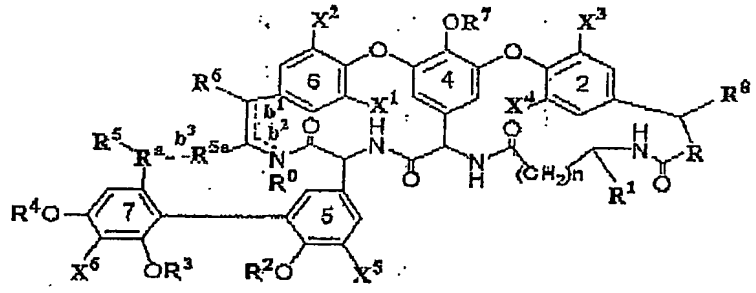
The present invention thus includes the use of selected compounds of the general formula I, II and III as an antiviral or to manufacture medicaments to treat or prevent antiviral infection, more preferably as a retroviral and more preferably as an anti-HIV and most preferably as an anti-HIV-1 or anti-HIV-2 compound. Such compounds can be natural glycopeptide antibiotics, with structures as for instance disclosed in K.C.Nicolaou, C.N.C. et al. Chem. Int. Ed., 1999, V.38, p.2096-2152 and B.Cavalleri & F.Parenti. Encyclopedia of Chemical Technology, 1992, V.2, p.995-1018.

The present invention, however, also provides new synthetic, semisynthetic or biosynthetic derivatives of natural glycopeptide antibiotics of the general formula I, II and III. These new compounds can be engineered to be inactive as antibacterials at therapeutic antiviral doses.

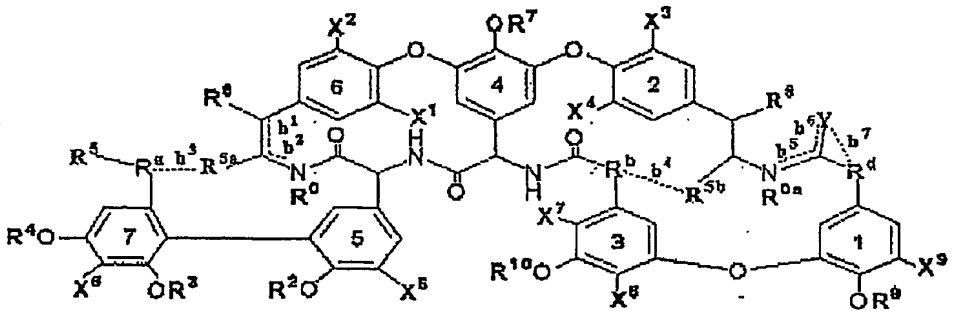
In a further preferred embodiment of present invention these antiviral compounds can be compounds of the formula I, II and III or salts thereof, wherein:

b^1 and b^2 each independently represents nihil or an additional bond, R^0 represents nihil when b^2 represents an additional bond and hydrogen when b^2 represents nihil, R^6 represents nihil when b^1 represents an additional bond and hydrogen when b^1 represents nihil, R^6 represents R^{6a} and R^0 represents hydrogen when b^1 and b^2 each represents nihil, wherein R^{6a} is described below. Preferably R^6 represents R^{6a}, R^0 represents hydrogen and b^1 and b^2 each represents nihil;

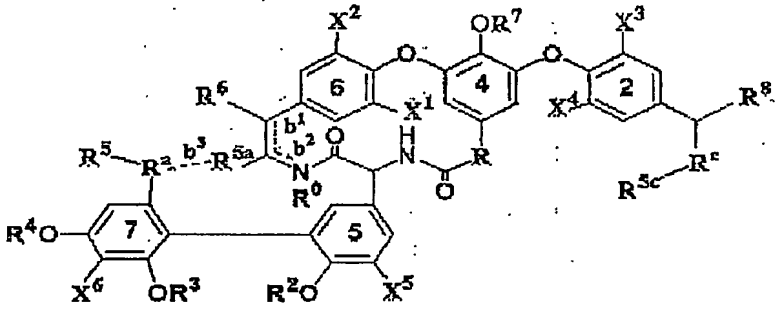
Formula I



Formula II



Formula III



b^3 represents nihil or an additional bond, R^a---R^{5a} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_zN(R^{11a})CO$ when b^3 represents an additional bond, and R^a is R and R^{5a} is R^5 when b^3 represents nihil, wherein z is 0, 1, 2, 3 or 4 and R, R^5, R^{11} and R^{11a} are described below. Preferably R^a---R^{5a} represents CHNHCO;

b^4 represents nihil or an additional bond, R^b---R^{5b} represents a group of the formula: $CHN(R^{11})CO$, $CHN(R^{11})(CH_2)_zN(R^{11a})CO$ or $CHN(R^{11})CO(CH_2)_pN(R^{11a})CO$ when b^4 represents an additional bond, and R^b is R and R^{5b} is R^5 when b^4 represents nihil, wherein p is 0, 1, 2, 3 or 4 and R, R^5 R^{11} and R^{11a} are described below;

b^5, b^6 and b^7 each independently represents nihil or an additional bond. Y represents oxygen, R^{0a} represents hydrogen and R^d represents R or a group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5 and b^7 represent nihil and b^6

represents an additional bond. R^{0a} represents nihil, R^d---Y represents a group of the formula: CHN=C(NR^{11})O or CHNHCON(R^{11}) when b^6 represents nihil and b^5 represents an additional bond. Y and R^{0a} each represents a hydrogen and R^d represents group of the formula: $(CH_2)_qCON(R^{11})CH(CH_2OH)$ $(CH_2)_qN(R^{12})CH(CH_2OH)$ when b^5, b^6 and b^7 each represents nihil, wherein q is 0, 1, 2, or 3 and R, R^{11} and R^{12} are described below;

n is 0, 1, 2 or 3;

X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen, halogen and X^6, wherein X^6 is defined below. Preferably X^1, X^2, X^3, X^4, X^5, X^7 and X^9 are each independently selected from hydrogen and Cl;

X^6 is selected from the group comprising hydrogen, halogen, SO_3H, OH, NO, NO_2, $NHNH_2$, $NHN=CHR^{11}$, $N=NR^{11}$, $CHR^{11}R^{13}$, $CH_2N(R^3)R^{11}$, R^5, R^{11} and R^{13}, wherein R^3 is CH_2 attached to phenolic hydroxyl group of the 7th amino acid, R^5, R^{11} and R^{13} are defined below. Preferably X^6 is CH_2R^{13};

X^8 is selected from hydrogen and methyl;

R^c represents R and R^{5c} represents R^5, wherein R and R^5 are defined below;

R is selected from CHR^{13} and R^{14}, wherein R^{13} and R^{14} are defined below. Preferably R is CHR^{13};

R^1 is selected from hydrogen and R^{11}, wherein R^{11} is defined below. Preferably R^1 is $(CH_2)_tCOOH$, $(CH_2)_tCONR^{11}R^{12}$, $(CH_2)_tCOR^{13}$, $(CH_2)_tCOOR^{11}$, COR^{15}, $(CH_2)_tOH$, $(CH_2)_tCN$, $(CH_2)_tR^{13}$, $(CH_2)_tSCH_3$, $(CH_2)_tSOCH_3$, $(CH_2)_tS(O)_2CH_3$, $(CH_2)_t$phenyl(*m*-OH, *p*-Cl), $(CH_2)_t$phenyl(*o*-X^7, *m*-OR^{10}, *p*-X^8)-[O-phenyl(*o*-OR^9, *m*-X^9, *m*-R^{16})]-*m*, where t is 0, 1, 2, 3 or 4. R, X^7, X^8, X^9 are defined above. R^{11}, R^{12}, R^{13}, R^{15} and R^{16} are defined below;

R^2 and R^4 are each independently selected from hydrogen, R^{12} and R^{17}, wherein R^{12} and R^{17} are defined below;

R^3 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or O-acetylmannosyl. R^{12} and R^{17} are defined below;

R^5 is selected from COOH, $COOR^{11}$, COR^{13}, COR^{15}, CH_2OH, CH_2halogen, CH_2R^{13}, CHO, $CH=NOR^{11}$, $CH=NNR^{11}R^{12}$ and $C=NNHCONR^{11}R^{12}$, wherein R^{11}, R^{12}, R^{13} and R^{15} are defined below;

R^{6a} is selected from OR^{12}, OR^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, ristosaminyl, N-acetylglucosaminyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, glucuronyl, 4-

oxovancosaminyl, ureido-4-oxovancosaminyl and their derivatives with functional groups such as, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^7 is selected from hydrogen, R^{12}, R^{17}, Sug and alkyl-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is glucosyl, mannosyl, ristosaminyl, N-acylglucosaminyl, N-acylglucuronyl, glucosaminyl, glucuronyl, 4-*epi*-vancosaminyl, 3-*epi*-vancosaminyl, vancosaminyl, actinosaminyl, acosaminyl, glucosyl-vancosaminyl, glucosyl-4-*epi*-vancosaminyl, glucosyl-3-*epi*-vancosaminyl, glucosyl-acosaminyl, glucosyl-ristosaminyl, glucosyl-actinosaminyl, glucosyl-rhamnosyl, glucosyl-olivosyl, glucosyl-mannosyl, glucosyl-4-oxovancosaminyl, glucosyl-ureido-4-oxovancosaminyl, glucosyl(rhamnosyl)-mannosyl-arabinosyl, glucosyl-2-O-Leu and their derivatives with as functional groups, for example, amino, carboxy, hydroxy and oxo. Typical carbohydrate derivatives comprising $NR^{11}R^{12}$, $N^+R^{11}R^{11a}R^{11b}$, $COOR^{11}$, COR^{13}, COR^{15}, $O\text{-}R^{12}$, $O\text{-}R^{17}$, $C{=}NOR^{11}$, $CHNHOR^{11}$, $C{=}NNR^{11}R^{12}$ and $C{=}NNHCONR^{11}R^{12}$ derivatives, wherein R^{11}, R^{11a}, R^{11b}, R^{12}, R^{13}, R^{15} and R^{17} are defined below;

R^8 is selected from hydrogen, R^{12}, R^{17}, OH, O-alkyl-Sug and O-Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is O-mannosyl, O-galactosyl and O-galactosyl-galactosyl;

R^9 is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is galactosyl or galactosyl-galactosyl. R^{12} and R^{17} are defined below;

R^{10} is selected from hydrogen, R^{12}, R^{17} or Sug, wherein Sug is any cyclic or acyclic carbohydrate. Preferably Sug is mannosyl or fucosyl. R^{12} and R^{17} are defined below;

R^{11}, R^{11a} and R^{11b} are each independently selected from the group consisting of hydrogen, alkyl, aryl, heteroaryl, cyloalkyl, heterocycloalkyl;

R^{12} and R^{12a} are each independently selected from the group consisting of hydrogen, alkyl, cycloalkyl, aryl, heterocycloalkyl, heteroaryl, acyl, amino-protecting group, carbamoyl, thiocarbamoyl, SO_2R^{11}, $S(O)R^{11}$, $COR^{13}\text{-}R^{18}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}NR^{11}R^{12}$ and $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above, R^{13} and R^{18} are defined below. Preferably R^{12a} is hydrogen, $COCHR^{18}NR^{11}R^{12}$, $COCHR^{18}N(NO)R^{11}$, $COCHR^{18}N^+R^{11}R^{11a}R^{11b}$ and $COCHR^{18}R^{13}$;

R^{13} is selected from the group consisting of hydrogen, NHR^{12a}, $NR^{11}R^{12}$, $NR^{11}Sug$, $N^+R^{11}R^{11a}R^{11b}$, R^{15}, $NR^{11}C(R^{11a}R^{11b})COR^{15}$ and group of the formula:

N- A- N^+- A

wherein A is $-CH_2-B-CH_2-$ and B is $-(CH_2)_m-D-(CH_2)_r-$, wherein m and r are from 1 to 4 and D is O, S, NR^{12}, $N^+R^{11}R^{11a}$, wherein Sug is any cyclic or acyclic carbohydrate, R^{11}, R^{11a} and R^{12} are defined above;

R^{14} is CH_2, C=O, CHOH, $C=NOR^{11}$, $CHNHOR^{11}$, $C=NNR^{11}R^{12}$, $C=NNHCONR^{11}R^{12}$ and $CHNHNR^{11}R^{12}$, wherein R^{11} and R^{12} are defined above;

R^{15} is selected from $N(R^{11})NR^{11a}R^{12}$, $N(R^{11})OR^{11a}$, $NR^{11}C(R^{11a}R^{11b})COR^{13}$, wherein R^{11}, R^{11a}, R^{11b}, R^{12} and R^{13} are defined above;

R^{16} is selected from group of the formula: R-R^5 or $CH(NH_2)CH_2OH$;

R^{17} is selected from SO_3H, $SiR^{11}R^{11a}R^{11b}$, $SiOR^{11}OR^{11a}OR^{11b}$, $PR^{11}R^{11a}$, $P(O)R^{11}R^{11a}$, $P^+R^{11}R^{11a}R^{11b}$, wherein R^{11}, R^{11a} and R^{11b} are defined above;

R^{18} is selected from hydrogen and R^1, wherein R^1 is defined above. Preferably R^{18} is CH_3, $CH_2CH(CH_3)_2$, phenyl(*p*-OH, *m*-Cl), phenyl-rhamnose-*p*, phenyl-(rhamnose-galactose)-*p*, phenyl-(galactose-galactose)-*p*, phenyl-O-methylrhamnose-*p*;

Each compound of the present invention may be a pure stereoisomer coupled at each of its chiral centers or it may be inverted at one or more of its chiral centers. It may be a single stereoisomer or a mixture of two or more stereoisomers. If it is a mixture, the ratio may or may not be equimolar. Preferably the compound is a single stereoisomer. Preferably the stereochemistry of the peptide core of the compound containing six amino acids (2-7) is 2(*R*), 3(*S*), 4(*R*), 5(*R*), 6(*S*) and 7(*S*).

Yet another embodiment of present invention is the use of one or more compounds of the formulas I, II or III in a pharmaceutical composition to treat or prevent a viral infection, preferably retroviral infection and yet more preferably a HIV-1 or HIV-2 infection. Thus, one or more of the compounds, preferably in the form of a pharmaceutically acceptable salt, can be formulated for oral or parenteral or topical administration for therapeutic or prophylactic treatment a viral infection, preferably of retroviral infection and yet more preferably of HIV infections.

For example: the compound can be mixed with pharmaceutically acceptable carriers and excipients and used in the form of tablets, capsulas, elixirs, suspensions, gels, syrups, wafers

and the like. The compositions comprising one or more compounds of the general formula I, II or III or derivatives of these compound will contain from about 0.01 to about 90 % by weight of the active compound, and more prefereably from about 10 to about 30 %. The composition may contain pharmaceutical acceptable carriers and excipients, such as corn starch, or gelatin, lactose, sucrose, microcrystalline cellulose, dicalcium phosphate, sodium rilloride, and alginic acid.

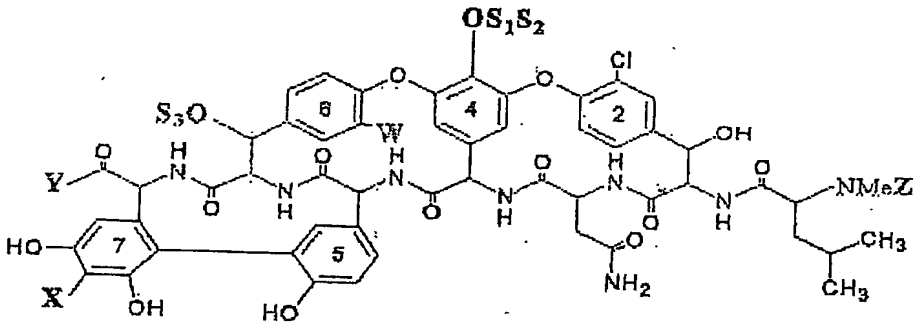
For intravenous use, a water soluble form of the compounds of present invention can be dissolved in one of the commonly used intravenous fluids or any pharmaceutically acceptable fluid for intravenous injection and administered by infusion. Such fluids as, for example, physiological saline, Ringer's solution, or % dextrose solution can be used. For intramuscular preparation, a sterile formulation of a suitable soluble salt form of the compound, for example a hydrochloride salt, can be dissolved and administered in a pharmaceutical diluent such as pyrogen-free water (distilled), physiological saline or 5 % glucose solution. A suitable insoluble form of the compound may be prepared and administered as a suspension in an adequate base or a pharmacologically acceptable oil base, for example, an ester of a long chain fatty acid such as ethyl oleate. For topical (i.e. intravaginal) use, a sterile formulation of a suitable form of the compound can be incorporated in a gel or a cream or alike.

Examples

5

Examples

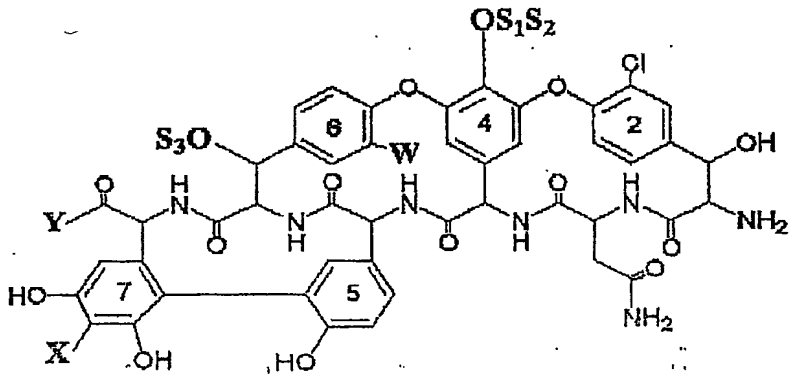
Scheme 1. Vancomycin and eremomycin derivatives



Code no.	X	Y	Z	Brutto formula	MW Calc.
Vancomycin derivatives W=Cl, S_1=Glu, S_2=vancosamine, S_3=H					
1	$CH_2N[CH_2CH_2]_2$ NBnBu-p	OH	H	$C_{82}H_{99}N_{11}O_{24}Cl_2$	1694
Eremomycin derivatives W=H, S_1=Glu, S_2=S_3=eremosamine					
2	$CH_2NHBnBu$-p	NHMe	H	$C_{86}H_{108}N_{12}O_{25}Cl$	1727
Eremomycin aglycon derivatives W=S_1=S_2=S_3=H					
3	$CH_2N[CH_2CH_2]_2$ NBnPh-p	OH	H	$C_{71}H_{75}N_{10}O_{17}Cl$	1374
4	$CH_2N[CH_2CH_2]_2N$ BnPh-p	NHMe	Boc	$C_{77}H_{86}N_{11}O_{18}Cl$	1487
5	$CH_2N[CH_2CH_2]_2N$ BnPh-p	NHMe	H	$C_{72}H_{78}N_{11}O_{16}Cl$	1387
6	H	$NHCH_2$(Adam-1)	H	$C_{54}H_{70}N_9O_{16}Cl$	1255

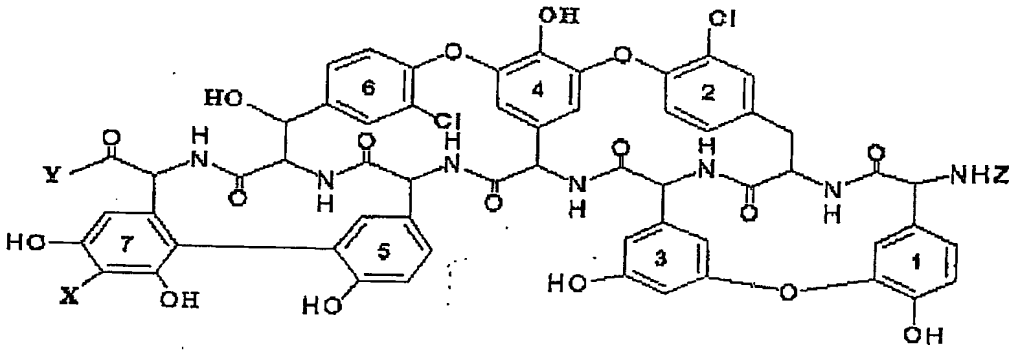
7	H	NHBn-F-p	H	$C_{60}H_{59}N_9O_{16}FCl$	1215
8	H	perhydroiso-quinol-1-yl	H	$C_{62}H_{68}N_9O_{16}Cl$	1229
9	H	$N(C_6H_{11})CONH$-C_6H_{11}	H	$C_{66}H_{75}N_{10}O_{17}Cl$	1314

Scheme 2. Eremomycin hexapeptide derivative



Des-(N-methyl-D-leucyl)-eremomycin aglycon (hexapeptide)					
W=S_1=S_2=S_3=H					
10	$CH_2NHAdam$	NHMe	-	$C_{58}H_{60}N_8O_{15}Cl$	1143

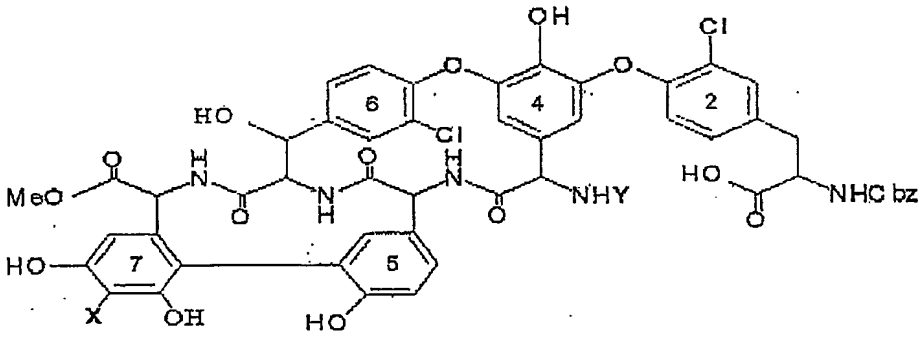
Scheme 3. Teicoplanin aglycon derivatives.



No	X	Y	Z	Brutto formula	MW
Teicoplanin aglycon (TD) derivatives					
11	H	$N(CH_2)_3NCOC_9H_{19}$	H	$C_{72}H_{71}N_9O_{18}Cl_2$	1448
12	H	$NH(CH_2)_6NH_2$	H	$C_{64}H_{59}N_9O_{17}Cl_2$	1297
13	$CH_2NH(CH_2)_3N^+Me_2C_{10}H_{21}$	$NH(CH_2)_6NH_2$	H	$C_{80}H_{94}N_{11}O_{17}Cl_2$	1552
14	H	$NH(CH_2)_{10}NH_2$	H	$C_{68}H_{67}N_9O_{17}Cl_2$	1353
15	H	$NH(CH_2)_5CO$-D-Ala-D-Ala	Boc	$C_{75}H_{74}N_{10}O_{23}Cl_2$	1554
16	CH_2NHMe	NHMe	H	$C_{61}H_{53}N_9O_{17}Cl_2$	1255

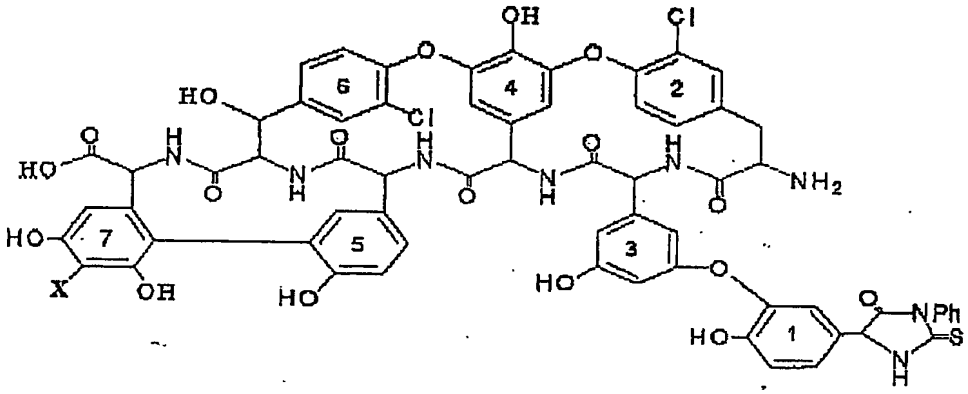
17	H	$N[CH_2CH_2]_2N$ $COCH_2NHBnBu\text{-}p$	H	$C_{75}H_{70}N_{10}O_{18}Cl_2$	1470
18	$CH_2NHBnBu\text{-}p$	NHMe	Boc	$C_{76}H_{73}N_9O_{19}Cl_2$	1487
19	$CH_2NHBnBu\text{-}p$	NHMe	H	$C_{71}H_{65}N_9O_{17}Cl_2$	1387
20	H	OH	Adoc	$C_{69}H_{59}N_7O_{20}Cl_2$	1377
21	H	NHAdam	H	$C_{68}H_{60}N_8O_{17}Cl_2$	1332
22	$CH_2NHAdam$	NHMe	H	$C_{70}H_{65}N_9O_{17}Cl_2$	1375
23	$CH_2NHAdam$	NHAdam	H	$C_{79}H_{77}N_9O_{17}Cl_2$	1495
24	H	$N(CH_3)CH(Adam\text{-}1)$	H	$C_{70}H_{64}N_8O_{17}Cl_2$	1359
25	H	NHBn-F-p	H	$C_{63}H_{51}N_8O_{17}FCl_2$	1304
26	H	$NHCH_2(Adam\text{-}1)$	H	$C_{69}H_{62}N_8O_{17}Cl_2$	1344
27	H	$N(C_6H_{11})CONH\text{-}C_6H_{11}$	H	$C_{71}H_{67}N_9O_{18}Cl_2$	1403

Scheme 4. Modified products of teicoplanin aglycon degradation



Compound 28. X = $CH_2NHAdam$, Y = Boc; $C_{67}H_{68}N_6O_{18}Cl_2$, 1315

Compound 29. X = $CH_2NHAdam$, Y = H; $C_{62}H_{60}N_6O_{16}Cl_2$, 1215



Compound 30. X = $CH_2NHAdam$, $C_{76}H_{68}N_9O_{18}Cl_2S$, 1498

Footnote: Adam: Adamant-1-yl.

METHODS OF SYNTHESIS

Method A. Aminomethylated derivatives (1, 3, 28, 29, 30)

To a stirred solution of 0.5 mmol of antibiotic or its degradation product and 4 mmol of an appropriate amine in 10 ml of an acetonitrile-water 1 : 1 mixture was added 3 mmol of 37% aquous formaldehyde. If a salt of amine was used 1n NaOH was added to pH 10. The reaction mixture was stirred at room temperature for 18 h and then 100 ml of water was added. After adjusting the reaction mixture at pH 3 with 1n HCl, the resulting solution (or suspension) was extracted with *n*-BuOH (~ 25 ml x 2); the organic layer was washed with water (~ 15 ml x 2) and then concentrated at 45 °C in a vacuum to a small volume (~3 ml). On adding ether (~ 100 ml), the precipitated solid was collected and dried in vacuum at room temperature for 4 h. Then it was dissolved in a minimal amount of MeOH and applied to a chromatographic column with Sephadex LH-20 (2 x 100 cm) preequilibratedbwith MeOH. The column was developed with MeOH at a rate of 10 ml/h, while collecting 5 ml fractions. The suitable fractions were combined and concentrated to a small volume (~ 3 ml). After adding ether (~ 100 ml) the precipitate formed was collected, rinsed with ether and dried in vacuum at room temperature.

The starting compound for **28** – N^2-Cbz-N^4-Boc-TDTP-Me - was obtained as previously described [1]. Compound **29** was obtained from **28** by the removal of Boc-group in TFA as previously described for N^2-Cbz-N^4-Boc-TDTP-Me[1].

The starting compound for **30** – N-terminal phenylthiohydantoin-derivative of teicoplanin aglycon – was obtained by Edman degradation of teicoplanin aglycon.

1. Malabarba, A.; Ciabatti, R.; Maggini, M.; Ferrari, P.; Vekey, K.; Colombo, L.; Denaro, M. Structural modifications of the active site in teicoplanin and related glycopeptides.2. Deglucoteicoplanin-derived tetrapeptide. *J. Org. Chem.* **1996**, *61*, 2151–2157.

Method B. Carboxamides (6, 7, 8, 9, 11, 12, 14, 17, 21, 24, 25, 26, 27)

To a mixture of an antibiotic or its degradation product (0.5 mmol) and 5 mmol of an amine hydrochloride dissolved in 5 ml of DMSO were added portion-wise Et_3N to adjust pH 8.5-9 and afterwards during 1 hour 1 mmol of PyBOP - reagent (benzotriazol-1-yloxy)-tris-(pyrrolidino) phosphonium-hexafluorophosphate) or HBPyU-reagent (O-(benzotriazol-1-

yloxy)-N,N,N',N'-bis(tetramethylene)uronium hexafluorophosphate). The reaction mixture was stirred at room temperature for 3 hours.

Addition of ether (~100 ml) to the reaction mixture led to an oily residue, which was shaken successively with ether (15 ml x 2) and acetone (~15 ml). After addition of 100 ml of acetone a precipitate of crude amide was collected, dissolved in 50 ml of water and 1n NaOH was added to pH 9. The resulting solution (or suspension) was extracted with *n*-BuOH (~ 25 ml x 3); the organic layer was washed with water (~ 15 ml x 3) and then concentrated at 45 °C in vacuum to a small volume (~3 ml). On adding ether (~ 100 ml), the precipitated solid was collected and dried in a vacuum at room for 4 h. and 100 ml of acetone was added to form the precipitate, which was collected to give a pure carboxamide.

Method C. Carboxamides of aminomethylated derivatives (2, 5, 6, 9, 12, 15, 18, 19)

These compounds were obtained by the method B starting from the aminometylated derivatives obtained by the method A.

Method D. N-carbamoylated derivative. (20)

To a stirred solution of 0.5 mmol of antibiotic or its degradation product in 15 ml THF-water 1 : 1 mixture adjusted to pH 10 with 1n NaOH 0.55 mmol of adamantyloxycarbonyl chloride was added. The reaction mixture was stirred at room temperature for 4 h, then it was diluted with 100 ml of water. After adjusting the reaction mixture at pH 3 with 1n HCl, the resulting solution (or suspension) was extracted with *n*-BuOH (~ 25 ml x 2); the organic layer was washed with water (~ 15 ml x 2) and then concentrated at 45 °C in a vacuum to a small volume (~3 ml). On adding ether (~ 100 ml), the precipitated solid was collected and dried in vacuum at room temperature for 4 h.

Method E. N-carbamoylated derivative of carboxamide (15)

This compound was obtained by the method D using Boc_2O reagent starting from carboxamide obtained by the method B.

Method F. N-carbamoylated derivative of carboxamides of aminomethylated derivatives (4, 18)

These compounds were obtained by the method D using Boc_2O reagent starting from carboxamides of aminomethylated derivatives obtained by the method C.

Changing the nature of the sugar residues of the glycopeptide antibiotics such has vancomycin can be performed as described in Nicas, T.I. et al. (Antimicrobial agents and Chemotherapy,1996, 40, 2194-2199.)

Degradation products, the aglycon antibiotics can be obtained through chemical degradation as described as examples hereunder.

Eremomycin aglycon was obtained as described in Berdnikova, T.F. et al (Berdnikova, T.F.; Lomakina, N.N.; Olsufyeva, E.N.; Alexandrova, L.G.; Potapova, N.P.; Rozinov, B.V.; Malkova, I.V.; Orlova, G.I. Structure and Antimicrobial Activity of Products of Partial Degradation of Antibiotic Eremomycin. Antibiotics and Chemotherapy (Rus) 1991, 36, 28–31). 1000 mg (0.6 mmol) of eremomycin sulfate were dissolved in 20 ml of HCl (concentrated) and were kept at a room temperature for 5 h. Then 60 ml of water were added to precipitate eremomycin aglycon. The mixture was cooled to 5 ^{0}C and kept in refrigerator for 3 h. The solid was filtered off, washed with 10 ml of cool water, then with aceton and dried in vacuum. The solid was dissolved in 6 ml of DMSO and was added to 60 ml of acetone. The precipitate was filterred off, washed with aceton and dried to yield 530 mg of a crude eremomycin aglycon. The water filtrate was passed through column (2x10 cm) of Dowex 50x2 resin (H^+-form), which was washed with water and eluted with 50 ml of 0.25 N NH_4OH. The eluates were concentrated in vacuum with n-BuOH to minimal volume and precipitated with 50 ml acetone. The precipitate was collected, washed with acetone and dried in vacuum to give a crude eremomycin aglycon. The samples were analyzed by TLC on the Merck Silica Gel $60F_{254}$ plates in systems EtOAc-PrOH-25% NH_4OH 2:2:3 with UV control.

The solids were combined and dissolved in 10 ml of 0.05 M $AcONH_4$-EtOH 9:1 mixture while acidified with 2 N HCl to pH 3 and applied to a chromatographic column with CM 32 carboxymethyl cellulose (Whatman, Greate Britane) (45 cm x 2 cm) preequilibrated with 0.05 M $AcONH_4$-EtOH 9:1 mixture (pH 6.7). The column chromatography was carried out with 0.05 M $AcONH_4$-EtOH 9:1 mixture (pH 6.7) (300 ml), 0.1 M $AcONH_4$-EtOH 9:1 mixture (pH 6.7) (700 ml), then 0.15 M $AcONH_4$-EtOH 9:1 mixture (pH 6.7) (700 ml) at a flow rate 30 ml/h. The fractions containing eremomycin aglycon were combined, acidified with 6 N HCl to pH 3 and passed through column (2x10 cm) of Dowex 50x2 resin (H^+-form), which was washed with water and eluted with 50 ml of 0.25 N NH_4OH. The eluates were concentrated in vacuum with n-BuOH to minimal volume, acidified with 0.05 N HCl to pH 5 and precipitated

with 50 ml acetone. The precipitate was collected, washed with acetone and dried in vacuum to give 310 mg (0.28mmol) oferemomycin aglycon (46.7 %).

Des-(N-methyl-D-leucyl) eremomycin aglycon was obtained from eremomycin aglycon as described in Miroshnikova, O.V. et al. (Miroshnikova, O.V.; Berdnikova, T.F.; Olsufyeva, E.N.; Pavlov, A.Y.; Reznikova, M.I.; Preobrazhenskaya, M.N.; Ciabatti, R.; Malabarba, A.; Colombo, L. A Modification of the N-Terminal Amino Acid in the Eremomycin Aglycone. J. Antibiot. 1996, 49, 1157–1161.

Teicoplanin aglycon was obtained as described in Malabarba, A. et al. (Malabarba, A.; Ferrari, P.; Gallo, G.G.; Kettenring, J.; Cavalleri, B. Teicoplanin, Antibiotics from Actinoplanes teichomyceticus nov. sp. VII. Preparation and NMR Characteristics of the Aglycone of Teicoplanin. J. Antibiotics 1986, 39, 1430-1442). The starting compound N-terminal phenylthiohydantoin-derivative of teicoplanin aglycon, was obtained by Edman degradation of teicoplanin aglycon. To a solution of teicoplanin aglycon (100mg, ~0.08 mmol) in a mixture of Py/H_2O (6:1, 4 mL), triethyl amine (0.26 mL, 2 mmol) and PhNCS (0.02 mL, ~0.16 mmol) were added at room temperature under argon. The reaction mixture was stirred for 16 h, then 8 mL of H_2O were added and the reaction mixture was evaporated with n-BuOH to dryness. The precipitate was dissolved in the mixture of TFA-CH_2Cl_2, 1:1 (3 mL) at 0–5 °C and then was stirred at this temperature for 1h. Water (3 mL) was then added and the mixture was neutralized with 25 % NH_4OH, washed with EtOAc (3 mL x 3), and the aqueous fraction was concentrated in vacuum with the addition of n-BuOH and applied to a column of silanized silica gel (2 x 100 cm), previously equilibrated with 0.01M acetic acid. The column was eluted with acetic acid (0.01M) at a flow rate of 30 mL/h for elution of compound N-terminal phenylthiohydantoin-derivative of teicoplanin aglycon. Fractions were pooled, concentrated with the addition of n-BuOH in vacuum, and acetone (50 mL) was added to yield the precipitate, which was filtered off, washed with acetone and dried to yield 68 mg (54 %).

The homogeneity and identity of the compounds obtained was assessed by HPLC and ESI mass-spectrometry. Analytical reverse phase HPLC was carried out on a Shimadzu HPLC instrument of the LC 10 series on a Diasorb C16 column (particle size 7 μm) at an

injection volume of 10 µL and a wave length 280 nm. The sample concentration was 0.05–0.2 mg/mL. Mass spectra were determined by Electrospray Ionisation (ESI) on a Finnigan SSQ7000 single quadrupole mass spectrometer.

ANTIVIRAL AND CYTOSTATIC ASSAY METHODS

Anti-HIV activity assays

Inhibition of HIV-1(III_B) and HIV-2(ROD)-induced cytopathicity in CEM cells was measured in microtiter 96-well plates containing ~3 x 10^5 CEM cells/ml, infected with 100 $CCID_{50}$ of HIV per ml and containing appropriate dilutions of the test compounds. After 4 to 5 days of incubation at 37°C in a CO_2-controlled humidified atmosphere, CEM giant (syncytium) cell formation was examined microscopically. The EC_{50} (50% effective concentration) was defined as the concentration of compound required to inhibit HIV-induced giant cell formation by 50%.

Cytostatic activity assays

All assays were performed in 96-well microtiter plates. To each well were added 5 – 7.5 x 10^4 cells and a given amount of the test compound. The cells were allowed to proliferate for 48 h (murine leukemia L1210) or 72 h (human lymphocyte CEM and Molt4/clone 8) at 37°C in a humidified CO_2-controlled atmosphere. At the end of the incubation period, the cells were counted in a Coulter counter. The IC_{50} (50% inhibitory concentration) was defined as the concentration of the compound that reduced the number of cells by 50%.

Discussion

A variety of glycopeptide antibiotic derivatives of vancomycin, eremomycin and teicoplanin including their aglycon derivatives were evaluated on their inhibitory activity against HIV-1(III_B) and HIV-2(ROD) in CEM cell cultures.

In contrast with vancomycin and eremomycin that did not show anti-HIV activity at 250 μM, the vancomycin derivative **1** modified at X (Scheme 1) was inhibitory to HIV-1 at an EC_{50} of 12 μM and to HIV-2 at an EC_{50} of 22 μM (Table 1). The eremomycin derivative **2** was 2-fold more inhibitory to HIV-1 than **1**. Interestingly, the eremomycin aglycon derivatives **3** to **5** all invariably inhibited both HIV-1 and HIV-2 at EC_{50} values ranging between 3.5 and 12.5 μM. This is at compound concentrations that were at least 15- to 20-fold lower than required for eremomycin aglycon. They were relatively non-toxic (IC_{50} > 100 μM-500 μM for CEM cells). The Des-(N-methyl-D-leucyl)-eremomycin aglycon **10** was also active against HIV (13-20 μM) and not toxic at 250 μM (Scheme 1, Table 1).

A large variety of teicoplanin aglycon derivatives have also been synthesized (Scheme 2) and evaluated for their anti-HIV activity (Table 1). All of them showed pronounced anti-HIV-1 and anti-HIV-2 activity, often with a trend of being slightly more active against HIV-1 than HIV-2. The most active congeners were inhibitory against HIV-1 in the range of 1.5 to 2.5 μM (compounds **11**, **13** and **23**). **23** was not cytotoxic at 250 μM. This means that **23** had a selectivity index (ratio IC_{50}/EC_{50}) that was ≥ 100. The antiviral activity of the latter compound was also at least 10-fold improved over the unsubstituted teicoplanin aglycon (EC_{50}: 17-20 μM; IC_{50}: > 500 μM).

Compounds **28** and **29** that lack the ring systems 1 and 3 and have only two macroring structures showed activity against HIV-1 and HIV-2 between 17 and 37 μM (Table 1, Scheme 3). Also, compound **30** (Scheme 4) showed an antiviral activity of 13 and 17 μM against HIV-1 and HIV-2, respectively (Table 1).

It is clear that in general, the aglycon derivatives of vancomycin, eremomycin and teicoplanin gain anti-HIV activity compared to their (usually inactive) glycosylated parent compounds. Also, substituents on the aglycons of vancomycin, eremomycin and teicoplanin that increase the lipophylicity of the aglycon antibiotic derivatives, markedly increase also the anti-HIV activity of the compounds. In some cases, just the simple aglycon showed already measurable anti-HIV activity, but hydrophobic derivatives were, as a rule, markedly more (10- to 100-fold) inhibitory to HIV. Among the teicoplanin derivatives, the highly hydrophobic

compound 17 shows prominent anti-HIV activity. The structural requirements to avoid cellular toxicity are unclear, but a number of antibiotic derivatives are clearly not cytostatic in cell culture, keeping pronounced antiviral activity.

In conclusion, novel classes of modified antibiotics have been discovered that were surprisingly active and selective against HIV in cell culture. The most active members of these antibiotic derivatives had an EC_{50} of 1-3 μM and were non-toxic in cell culture ($IC_{50} \geq 200$-500 μM). Their antiviral mechanism of action is located at an early event in the infection cycle of HIV (most likely adsorption and/or fusion), and clearly different from its molecular mechanism of anti-bacterial activity. The compounds efficiently suppress drug-resistant HIV-1 strains (data not shown), and resistance development in cell culture is difficult to afford. Therefore, the (lipophylic) aglycon antibiotic derivatives should be regarded as interesting new lead drugs that should be further explored as antiretroviral (i.e. HIV) compounds for systemic use. In addition, their early intervention in the infection cycle of HIV also make these compounds potential candidate drugs for prevention of HIV spread [i.e. as a microbicide given through local (i.e. topical) administration (i.e. intravaginally)].

Table 1. Cytostatic and anti-HIV activity of glycopeptide antibiotic derivatives

Compound	IC_{50}[a] (μM)			EC_{50}[b] (μM)	
No.	L1210	Molt4/C8	CEM	HIV-1	HIV-2
Vancomycin	> 500	> 500	> 500	> 250	> 250
Eremomycin	500	> 500	> 500	> 250	> 250
Teicoplanin	> 500	> 500	> 500	18 ± 3.5	100 ± 0
Teicoplanin aglycon	> 500	> 500	> 500	17 ± 3.5	20 ± 0
Eremomycin aglycon	> 500	> 500	> 500	50 ± 28	250 ± 0.0
Vancomycin aglycon	> 500	> 500	> 500	65 ± 7.1	250 ± 0.0
1	53 ± 9	> 100	> 100	12 ± 3.5	22 ± 3.5
2	22 ± 0.3	24 ± 18	95 ± 14.1	5.1 ± 3.3	20

3	250 ± 39	> 500	> 500	5.5 ± 0.7	12 ± 3.5
4	84 ± 22	> 100	> 100	4.0 ± 0	3.5 ± 0.7
5	> 100	> 100	> 100	4.0 ± 1.7	5.5 ± 0.7
6	94 ± 15	126 ± 11	148 ± 3	1.6 ± 0.36	7.0 ± 0.0
7	> 250	> 250	> 250	41.7 ± 20.2	> 125
8	> 250	> 250	> 250	63.3 ± 53.5	> 125
9	> 250	> 250	> 250	7.5 ± 4.8	32.5 ± 3.5
10	> 250	> 250	> 250	13 ± 9.9	20 ± 7.1
11	38.7 ± 3.4	32.3 ±	44 ± 0.42	1.5 ± 0.7	4.5 ± 2.1
12	> 500	> 500	> 500	15 ± 0	17.5 ± 3.5
13	38 ± 1	72 ± 6	66 ± 2	1.8 ± 0.49	7 ± 0
14	≥ 500	225 ± 8	402 ± 138	6.5 ± 0.7	12.5 ± 3.5
15	> 500	> 500	> 500	12.5 ± 3.5	25 ± 7
16	> 500	> 500	> 500	15 ± 7.1	17.5 ± 10.6
17	> 100	> 100	> 100	4 ± 0	7 ± 4.2
18	70 ± 23	> 100	> 100	6 ± 1	12 ± 5.2
19	> 100	> 100	> 100	9.7 ± 9	12.3 ± 6.8
20	22 ± 0.1	25 ± 0.99	104 ± 3.0	13 ± 9.9	6.0 ± 1.4
21	30 ± 5.7	26 ± 6.0	123 ± 6.0	7.0 ± 4.2	6.0 ± 1.4
22	212 ± 54	> 250	> 250	5.0 ± 1.4	17 ± 3.5
23	202 ± 68	> 250	> 250	2.5 ± 0.7	3.5 ± 2.1
24	92 ± 5	97 ± 10	106 ± 0	3.3 ± 1.4	7.5 ± 0.7
25	240 ± 15	≥ 250	> 250	9.0 ± 5.3	30.0 ± 7.1
26	91 ± 2	112 ± 2	125 ± 30	1.8 ± 0.58	7.0 ± 0.0
27	130 ± 1	132 ± 9	165 ± 34	6.0 ± 2.6	10.0 ± 2.8
28	95 ± 10	122 ± 13	240 ± 13	17 ± 3.5	11 ± 5.7
29	181 ± 4.0	> 250	> 250	17 ± 3.5	37 ± 18
30	73 ± 24	≥ 250	242 ± 11	13 ± 9.9	17 ± 3.5

[a]IC_{50}, or compound concentration required to inhibit tumor cell proliferation by 50%.

[b]EC_{50}, or compound concentration required to inhibit HIV-induced giant cell formation in CEM cell cultures by 50%.

Abstract

Glycopeptidic Compounds

Novel classes of modified antibiotics have been discovered that were surprisingly active and selective against HIV in cell culture. The most active members of these antibiotic derivatives had an EC_{50} of 1-3 μM and were non-toxic in cell culture ($IC_{50} \geq 200$-500 μM). Their antiviral mechanism of action is located at an early event in the infection cycle of HIV (most likely adsorption and/or fusion), and clearly different from its molecular mechanism of anti-bacterial activity. The compounds efficiently suppress drug-resistant HIV-1 strains, and resistance development in cell culture is difficult to afford.